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Synthetic Studies on Lythraceae Alkaloids. II.[1] The Mannich Reaction of Isopelletierine with 3-Methoxybenzaldehyde and 3-Hydroxybenzaldehyde[2]

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The Mannich reaction of isopelletierine (III) with 3-methoxybenzaldehyde (VI) in aqueous sodium hydroxide afforded the *trans*- and *cis*-quinolizidine (VIII and IX) in the 1:6 ratio, whereas the reaction with 3-hydroxybenzaldehyde (VII) gave almost exclusively the *trans*-quinolizidine (X). On the other hand, the reaction with VI in methanol afforded VIII and IX in the 6:1 ratio. On the basis of the detailed experiments the Mannich reaction of III with arylaldehyde under an alkaline condition was found to afford at first *cis*-4-arylquinolizidin-2-one, which then isomerized into the corresponding *trans*-isomer. And the stereoselectivity of this reaction was found to depend on solvents, solubilities of the starting arylaldehydes and products, and reaction times.

Lythraceae plants have been used as the medicine for dysentery, diarrhea, bronchitis, and syphilis.[4–6] And the beverage prepared from *Heimia salicifolia* is reported to produce a psychosomimetic effect.[5,6] From these plants more than twenty lactonic alkaloids have been hitherto isolated and established to possess the unique structures having a *trans*- or *cis*-quinolizidine ring with a biphenyl or biphenyl ether and a twelve- or fourteen-membered lactone, as shown in lythrine (I) and vertaline (II).[7,8]

One of the possible biosynthetic routes for Lythraceae alkaloids has been suggested[9] to be that *via* 4-arylquinolizidin-2-one (V) produced by the condensation of isopelletierine (III) with arylaldehyde (IV). Condensation of III with benzaldehyde has been reported to give a mixture of *trans*- and *cis*-4-phenylquinolizidin-2-one in the 1:2 ratio by Kaneko *et al.*,[10] whereas the reaction with isovanillin to give only *trans*-4-(3-hydroxy-4-methoxy)-phenylquinolizidin-2-one by Wróbel *et al.*[11] In order to obtain stereoselectively *trans*- and *cis*-quinolizidine derivatives for the total synthesis of Lythraceae alkaloids, the model experiments were carried out on these Mannich condensations.

The Mannich reaction of isopelletierine (III)[1] with 3-methoxybenzaldehyde (VI) in an aqueous sodium hydroxide solution, followed by chromatographic separation of the crude product afforded the quinolizidine (VIII), *m/e* 259 (M^+), and the isomeric quinolizidine (IX), *m/e* 259 (M^+), in 12% and 70% yield, respectively. The former (VIII) showed bands at 2790,

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2) A part of this work was reported at the 18th Symposium on the Chemistry of Natural Products, October 1974, Kyoto.
3) Location: *13-1, Takara-machi, Kanazawa, 920, Japan.*
4) Gougeon and Lanmonier, *J. Pharm. Chim.*, **17**, 397 (1918) [*Chem. Abstr.*, **12**, 2624 (1918)].
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8) Other type of Lythraceae alkaloids has been also isolated and characterized: E. Fujita and Y. Saeki, *J. Chem. Soc. Perkin I*, **1973**, 306 and references therein.
9) J.P. Ferris, C.B. Boyce, and R.C. Briner, *Tetrahedron Letters*, **1966**, 5129; S.H. Koo, R.N. Gupta, I.D. Spenser, and J.T. Wrobel, *Chem. Commun.*, **1970**, 396.
10) T. Matsunaga, I. Kawasaki, and T. Kaneko, *Tetrahedron Letters*, **1967**, 2471.
11) J.T. Wróbel and M.W. Gołębiewski, *Rocz. Chem.*, **45**, 705 (1971).

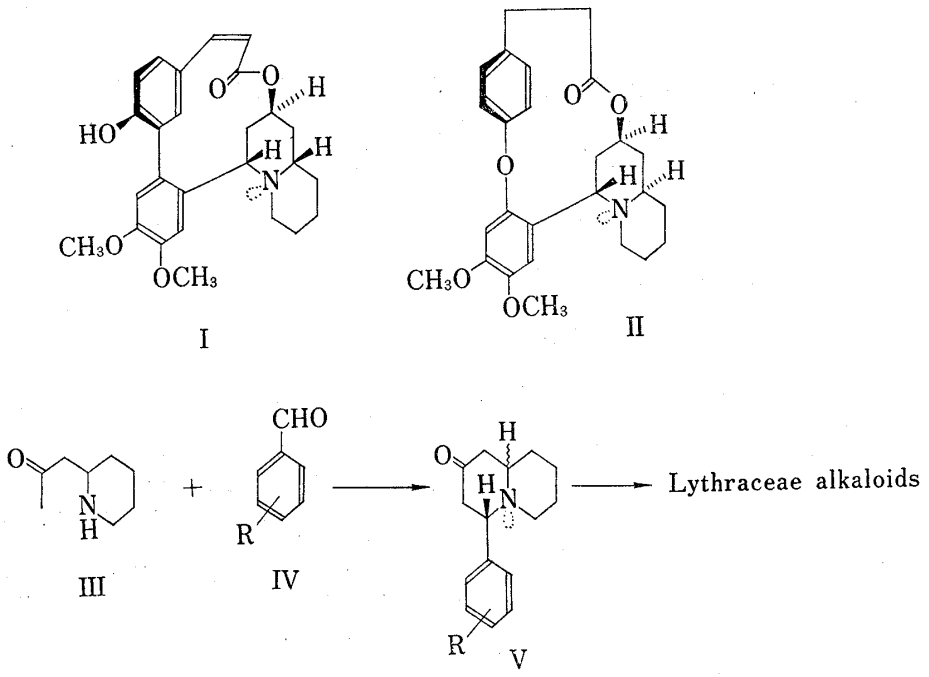

Chart 1

2750 (Bohlmann bands) and 1718 cm^{-1} (C=O) in its infrared (IR) spectrum and a signal due to C_4–H at 3.24 ppm as a doublet of doublets (J=11.5 and 3.5 Hz) in its nuclear magnetic resonance (NMR) spectrum. These physical data established the structure of VIII as the *trans*-fused quinolizidin-2-one with the equatorial aryl substituent at C-4 as depicted. The *cis*-fused quinolizidine structure of the latter (IX) was verified by the lack of Bohlmann bands in its IR spectrum and further by the chemical shift due to the axial proton at C-4 [4.21 ppm

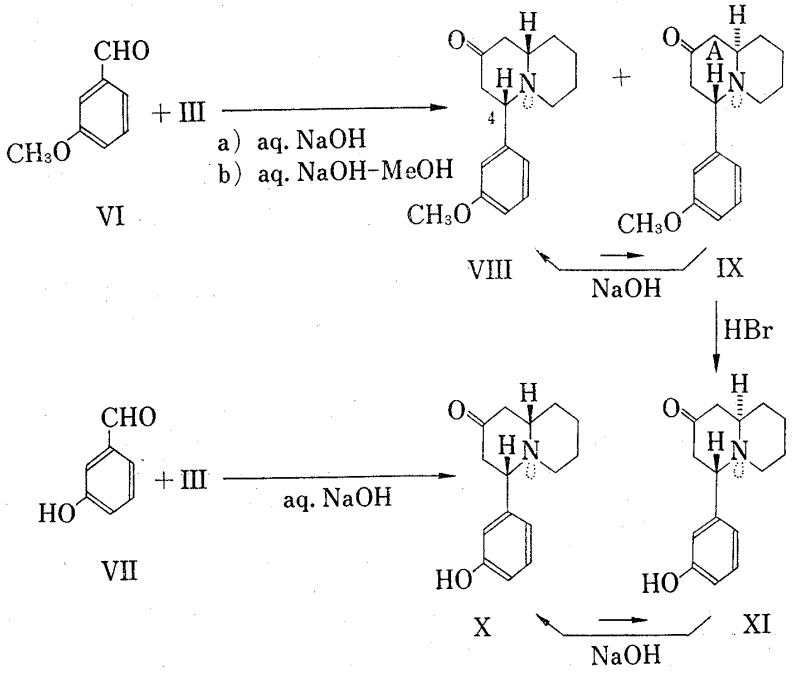

Chart 2

(d-d, J=6; 4.5 Hz)[12]] *ca.* 1 ppm lower[13] than that of the *trans*-quinolizidine (VIII) in its NMR spectrum.

On the other hand, on treatment of III with 3-hydroxybenzaldehyde (VII) in an aqueous sodium hydroxide solution, only the *trans*-quinolizidine (X), mp 155—156°, *m/e* 245 (M^+), could be isolated in 88% yield. In agreement with the stereostructure of X, the product showed bands at 3580, 3330 (OH), 2800, 2750 (Bohlmann bands), and 1716 cm^{-1} (C=O) in its IR spectrum and a signal at 3.14 ppm (d-d, J=11.5; 3 Hz, C_4–H) in its NMR spectrum. The other product was detected as a faint spot besides that of X in the thin-layer chromatography (TLC) of the crude product, but was too minor to be isolated.

Demethylation of the *cis*-quinolizidine (IX) with 48% hydrobromic acid provided in 70% yield the *cis*-isomer (XI), mp 153—154°, *m/e* 245 (M^+), which exhibited a signal at 4.11 ppm (d-d, J=6; 3.5 Hz,[12] C_4–H) in its NMR spectrum and no Bohlmann bands in its IR spectrum. This product was identical with the minor product described above in their TLC behavior.

Thus, the Mannich reaction of III with VI gave the *trans*- and *cis*-quinolizidine (VIII and IX) in the 1: 6 ratio, however, that with VII gave almost exclusively the *trans*-quinolizidine (X). These results together with those reported by Kaneko *et al.*[10] and Wróbel *et al.*[11] suggest that the solubilities of the starting arylaldehydes, as well as the products, govern the stereoselectivity of the reactions. Namely, the aldehyde (VI), insoluble in aqueous sodium hydroxide solution, was converted predominantly, to the *cis*-isomer, whereas the aldehyde (VII), soluble because of the presence of the phenolic hydroxyl group in its molecule, was converted to the *trans*-isomer.

On the above assumption the Mannich reaction of III with VI is anticipated to afford predominantly the *trans*-isomer (VIII) in the appropriate solvent which can dissolve VI. In fact, reaction of VI with III in methanol in the presence of aqueous sodium hydroxide yielded expectedly the *trans*- and *cis*-isomer (VIII and IX) in 77% yield in the 6: 1 ratio. But with monitoring by TLC it was observed that at the biginning of the reaction the *cis*-isomer was more produced than the *trans*-isomer and then the latter in comparison with the former increased gradually with lapse of time. This observation was confirmed by the product ratios of the *trans*- and *cis*-isomer obtained at various reaction times; ratio of *trans*-/*cis*-isomer (reaction time, hr): 4/17 (0.5), 2/3 (1), 6/7 (3), 7/3 (5).

The above results would be interpreted as follows; these Mannich reactions afforded at first the *cis*-isomer predominantly and then the *cis*-isomer isomerized to the stable *trans*-isomer by the action of base, especially in a soluble state. This interpretation was also supported by the isomerization experiments; the *cis*-quinolizidines (IX and XI) isomerized into the *trans*-quinolizidines (VIII and X), on treatment with sodium hydroxide in aqueous methanol and water, respectively. In these isomerizations the *cis*-isomers did not disappear completely, therefore the reaction might attain an equilibrium which lies extremely to the *trans*-isomers. Moreover, no isomerization would occur under an acidic condition, since demethylation of IX with hydrobromic acid did not afford the *trans*-quinolizidine (X).

The mechanism of the Mannich reaction of cyclohexanone with dimethylamine and formaldehyde in a basic medium has been proposed to be the S_N2 reaction of dimethylaminomethanol with the carbanion of cyclohexanone.[14] According to this mechanism, the present Mannich reaction should afford the *trans*-quinolizidine straightforward *via* the transition state (XII), but that would be in conflict with the above observation. A mechanism of these reactions which is compatible with the present observation would be postulated in Chart 3. Namely,

12) The small coupling constants of this proton in comparison with those of the corresponding *trans*-quinolizidine would indicate that the ring A of the *cis*-quinolizidine exists in a flexible form rather than a chair form.

13) F. Bohlmann D. Schumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.

14) T.F. Cumming and J.R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

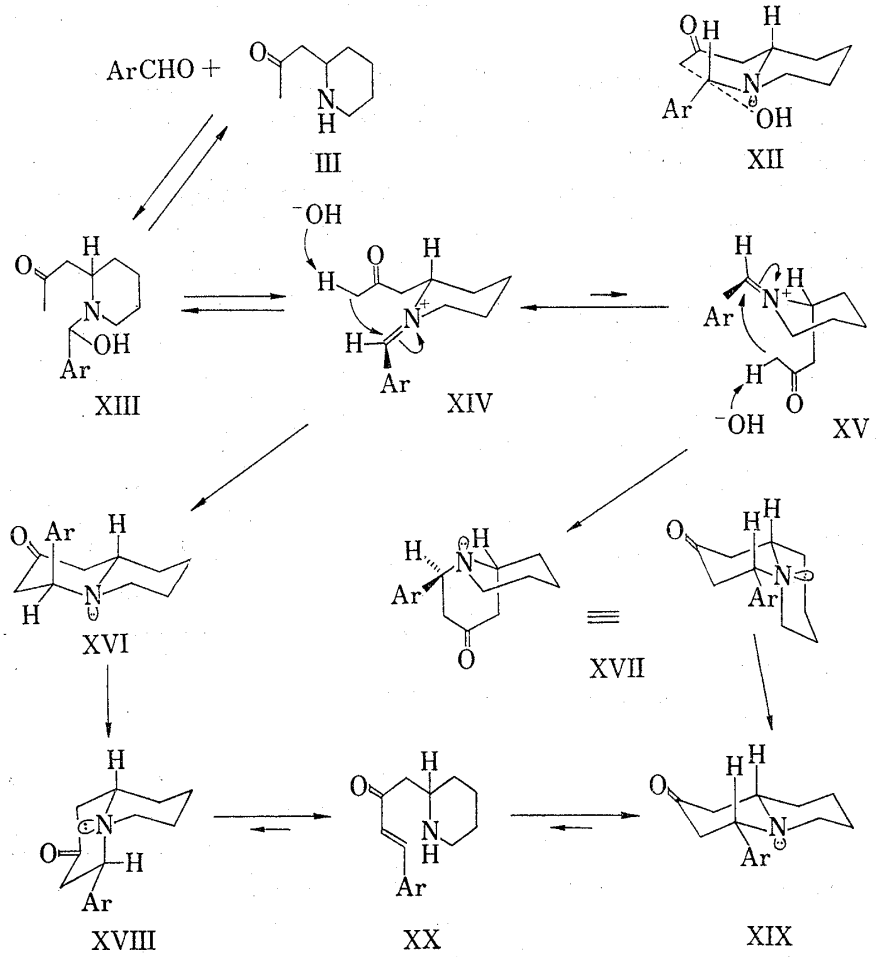

Chart 3

the aminoalcohol (XIII), formed by condensation of III with arylaldehyde, is equilibrated with the imminium salt (XIV), which is then transformed to the *cis*-quinolizidine (XVIII) *via* the unstable *trans*-quinolizidine (XVI) by the attack of hydroxide ion. On the other hand, the ring inversion of XIV gives the unstable conformer (XV), which can be similarly transformed to the *trans*-quinolizidine (XIX) *via* the unstable *cis*-quinolizidine (XVII). The former *via* XIV must be the preferred pathway. And the *cis*-quinolizidine (XVIII) comes to equilibrium with the *trans*-quinolizidine (XIX) *via* the unsaturated aminoketone (XX) by the action of hydroxide ion.

Thus, the Mannich reaction of isopelletierine with arylaldehyde under an alkaline condition was found to provide at first *cis*-4-arylquinolizidin-2-one, which then isomerized into the corresponding *trans*-isomer. Therefore, the stereoselectivity of this reaction was found to depend on solvents, solubilities of the starting arylaldehydes and the products, and reaction times.

Experimental[15]

4-(3-Methoxyphenyl) (*e*)-*trans*-quinolizidin-2-one (VIII) and 4-(3-Methoxyphenyl) (*e*)-*cis*-quinolizidin-2-one (IX)——1) In Water: A mixture of isopelletierine[1] (III, 950 mg), 3-methoxybenzaldehyde (VI, 800

15) Melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The extracts were dried over anhydrous Na_2SO_4. Alumina (Brockman grade II—III (Merck)) and silica gel (Wako gel Q-23, 100—200 mesh (Wako Ltd.)) were used for column chromatography. Alumina (Aluminiumoxid GF_{254} Typ E (Merck)) and silica gel (Kieselgel GF_{254} Typ 60 (Merck)) were used for TLC and preparative TLC (p-TLC). IR spectra were measured with IR-G, Japan Spectroscopic Co., NMR spectra with PS-100, Japan Electron Lab. Co., using tetramethylsilane (TMS) as an internal standard, mass spectra with JMS-01SG, Japan Electron Lab. Co., high resolution mass spectra with Hitachi RMU-7L.

mg), and 1% aq. NaOH (10 ml) was heated at 60° for 5 hr with stirring in a stream of N_2. The cooled reaction mixture was acidified with aq. HCl and washed with ether. The aqueous layer was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$–ether (3: 1) gave VIII (180 mg (12% based on VI)) as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2750 (Bohlmann bands), 1718 (C=O). NMR (in $CDCl_3$) δ: 3.81 (3H, s, OCH_3), 3.24 (1H, d-d, $J=11.5$; 3.5 Hz, C_4–H). Mass Spectrum *m/e*: 259 (M^+), 134 ($CH_3OC_6H_4$-$CHCH_2^+$), 84 (base peak, $C_5H_{10}N^+$). High resolution Mass Spectrum *m/e*: 259.1563. Calcd. for $C_{16}H_{21}O_2N$: 259.1571. Picrate: yellow prisms (C_6H_6), mp 168—170°. *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 54.09; H, 4.95; N, 11.47. Found: C, 54.28; H, 5.25; N, 11.23.

Elution with $CHCl_3$–MeOH (20: 1) gave IX (1.07 g (70% based on VI)) as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 4.21 (1H, d-d, $J=6$; 4.5 Hz, C_4-H), 3.78 (3H, s, OCH_3). Mass Spectrum *m/e*: 259 (M^+), 134 ($CH_3OC_6H_4CHCH_2^+$), 84 (base peak, $C_5H_{10}N^+$). High resolution Mass Spectrum *m/e*: 259.1590. Calcd. for $C_{16}H_{21}O_2N$: 259.1571. Picrate: yellow prisms (acetone), mp 172—174°. *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 54.09; H, 4.95; N, 11.47. Found: C, 54.08; H, 4.84; N, 11.65.

2) In Aqueous Methanol: A solution of III (600 mg), VI (500 mg), and 5% aq. NaOH (5 ml) in MeOH (15 ml) was heated at 70° for 6 hr with stirring in a stream of N_2. MeOH was evaporated and H_2O was added to the residue. The mixture was extracted with $CHCl_3$ and the extract was washed with H_2O, dried, and evaporated. The residue was treated in the same procedure as that described in 1) to give the *trans*-quinolizidine (VIII, 627 mg (66%)) and the *cis*-quinolizidine (IX, 105 mg (11%)), which were identical with VIII and IX obtained in 1), respectively, in IR spectra and TLC behavior.

3) Product Ratios of VIII and IX at Various Reaction Times in Aqueous Methanol: A solution of III (124 mg), VI (104 mg), and 5% aq. NaOH (1.0 ml) in MeOH (3.0 ml) was divided into four parts with the same volume (1.1 ml). They were heated at 70° for 0.5, 1, 3, and 5 hr, respectively. The reaction mixture of each part was treated in the same procedure as that described in 2) and the residue was separated by p-TLC (silica gel, ether) to give VIII and IX, which were identified with the corresponding authentic specimens in TLC behavior. The product ratios were as follows: VIII/IX mg (yield based on VI): 0.5 hr, 4 (7.5%)/17 (32%); 1 hr, 10 (19%)/16 (30%); 3 hr 13 (24.5%)/15 (28.5%); 5 hr, 23 (43.5%)/10 (19%).

4-(3-Hydroxyphenyl) (*e*)-*trans*-quinolizidin-2-one (X)——A solution of III (910 mg) and 3-hydroxybenzaldehyde (VII, 655 mg) in 5% aq. NaOH (5 ml) was heated at 60° for 6 hr with stirring in a stream of N_2. The reaction mixture was cooled and washed with ether. The aqueous layer was acidified with aq. HCl and washed with ether. The aqueous acidic layer was made alkaline to pH 8 with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was chromatographed on alumina with $CHCl_3$–MeOH (30: 1) as a solvent to give a crystalline product (X, 1.17 g (88% based on VII)), which was recrystallized from EtOH to give colorless plates, mp 155—156°. IR ν_{max}^{KBr} cm^{-1}: 3260 (OH), 2780, 2740 (Bohlmann bands), 1690 (C=O). $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3330 (OH), 2800, 2750 (Bohlmann bands), 1716 (C=O). NMR (in $CDCl_3$) δ: 6.26 (1H, br-s, OH), 3.21 (1H, d-d, $J=11.5$; 3 Hz, C_4–H). (d_6-DMSO) δ: 9.26 (1H, s, OH, disappeared by addition of D_2O), 7.04 (1H, t, $J=8$ Hz, aromatic C_5–H), 3.14 (1H, d-d, $J=11.5$; 3 Hz, C_4–H). Mass Spectrum *m/e*: 245 (M^+), 120 ($HOC_6H_4CHCH_2^+$), 84 (base peak, $C_5H_{10}N^+$). High resolution Mass Spectrum *m/e*: 245.1414. Calcd. for $C_{15}H_{19}O_2N$: 245.1415. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.38; H, 7.73; N, 5.52.

The another product was detected as a faint spot ($Rf=0.13$) besides that of X ($Rf=0.38$) on TLC (silica gel, $CHCl_3$–ether (1: 1)), but was too minor to be isolated, and identical with the *cis*-isomer (XI) in TLC behavior.

4-(3-Hydroxyphenyl) (*e*)-*cis*-quinolizidin-2-one (XI)——A solution of the *cis*-quinolizidine (IX, 330 mg) in 48% aq. HBr (15 ml) was heated at 110° for 4 hr. The cooled reaction mixture was made alkaline to pH 8 with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give a crystalline product (XI, 219 mg (70%)), which was recrystallized from MeOH to give colorless needles, mp 153—154°. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1719 (C=O). NMR (in d_6-DMSO) δ: 9.24 (1H, s, OH, disappeared by addition of D_2O), 7.02 (1H, t, $J=8$ Hz, aromatic C_5–H), 4.11 (1H, d-d, $J=6$; 3.5 Hz, C_4–H). Mass Spectrum *m/e*: 245 (M^+), 120 ($HOC_6H_4CHCH_2^+$), 84 (base peak, $C_5H_{10}N^+$). High resolution Mass Spectrum *m/e*: 245.1454. Calcd. for $C_{15}H_{19}NO_2$: 245.1415. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48: H, 7.79; N, 5.58.

Isomerization of IX into VIII——A solution of the *cis*-quinolizidine (IX, 40 mg) and 5% aq. NaOH (0.5 ml) in MeOH (5 ml) was heated at 70° for 6 hr with stirring. MeOH was evaporated and H_2O (2 ml) was added to the residue. The mixture was extracted with $CHCl_3$ and the extract was washed with H_2O, dried, and evaporated. The residue was separated by p-TLC (silica gel, ether) to give the *trans*-quinolizidine (VIII, 29 mg (73%)) and the *cis*-isomer (IX, 3.5 mg (9%)), which were identical with the corresponding specimens obtained above in IR spectra and TLC behavior.

The same isomerization reaction were carried out in the presence of 6-bromoisovanillin (35 mg). The products were VIII, IX, and 6-bromoisovanillin and its incorporation product could not be detected.

Isomerization of XI into X——A solution of the *cis*-quinolizidine (XI, 30 mg) in 2% aq. NaOH (5 ml) was heated at 60° for 5 hr with stirring. The cooled reaction mixture was made alkaline to pH 8 with aq.

HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was separated by p-TLC (silica gel, $CHCl_3$–ether (1: 1)) to give 3-hydroxybenzaldehyde (VII, 1 mg), the *trans*-quinolizidine (X, 18 mg (60%)), and the *cis*-isomer (XI, 0.5 mg), which were identical with the corresponding specimens obtained above in IR spectra and TLC behavior.

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